CHAPTER-3 Phase 3 Trial Design: Efficacy and Safety of the Oral Bradykinin B2 Receptor Antagonist Deucrictibant Extended-Release Tablet for Prophylaxis of Hereditary Angioedema Attacks

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Key takeaways

- CHAPTER-3 is an ongoing, global, Phase 3 study designed to evaluate the efficacy and safety of once-daily, oral deucrictibant extended-release (XR) tablet for prophylaxis of attacks in adolescents and adults with hereditary angioedema (HAE).
- Results from the Phase 2 CHAPTER-1 study support the CHAPTER-3 study design.

Deucrictibant	Primary efficacy endpoint	Safety endpoints	Patient-reported outcomes
XR Deucrictibant XR once-daily tablet	24 weeks Time-normalized number of investigator-confirmed HAE attacks during the 24-week treatment period	TEAEs, clinical laboratory tests, vital signs, and ECG parameters	Health-related quality of life, disease control, work productivity and activity impairment, and treatment satisfaction

ECG, electrocardiogram; HAE, hereditary angioedema; TEAE, treatment-emergent adverse event; XR, extended-release.

Background

- **Hereditary angioedema (HAE):** a rare genetic condition caused by excess bradykinin production and characterized by painful, often disabling, swelling attacks affecting multiple locations in the body.[1-3]
- **Unmet need:** additional prophylactic treatments offering injectable-like efficacy, a well-tolerated profile, and ease of administration.[4-7]
- **Deucrictibant:** deucrictibant is a selective, orally administered antagonist of the bradykinin B2 receptor under development for prophylactic and on-demand treatment of HAE attacks.[8-18]

Objective

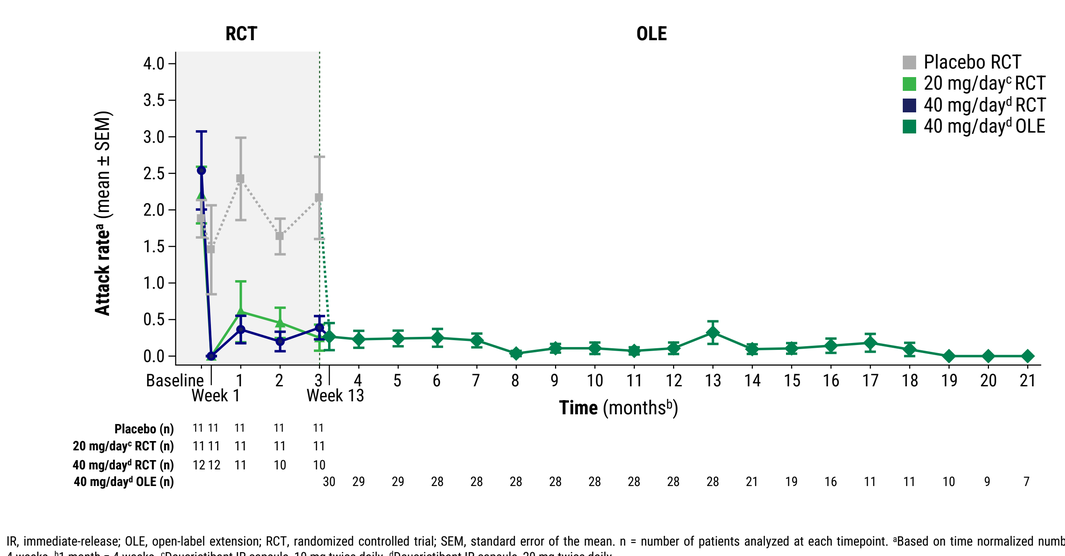
The CHAPTER-3 study (NCT06669754) is an ongoing, global, Phase 3 study designed to evaluate the efficacy and safety of once-daily, oral deucrictibant XR tablet for prophylaxis of attacks in adolescents and adults with HAE.

Previous studies

CHAPTER-1

- In the placebo-controlled, Phase 2 trial (NCT05047185), deucrictibant significantly reduced occurrence of attacks, induced clinically meaningful improvement in disease control and in health-related quality of life, and was generally well tolerated.[14,15]
- Attack rate was significantly reduced with deucrictibant in the randomized controlled trial (RCT) and remained low over long-term treatment in the open-label extension (OLE).
- The immediate-release (IR) capsule was dosed twice per day as a proof-of-concept for the once-daily deucrictibant XR tablet (intended formulation for prophylactic HAE treatment).
- CHAPTER-1 results supported further development of deucrictibant as a potential prophylactic treatment for HAE.[15]

Figure 1. Reduced attack rate by week 1 in the CHAPTER-1 RCT remained low in the OLE

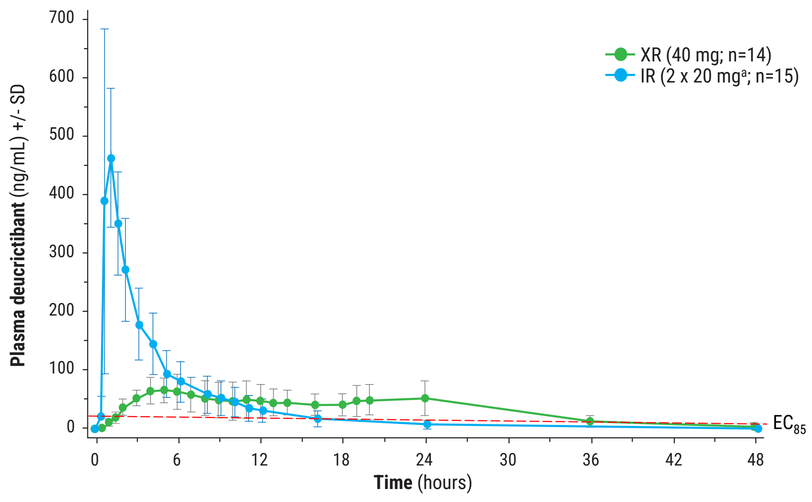


IR, immediate-release; OLE, open-label extension; RCT, randomized controlled trial; SEM, standard error of the mean. n = number of patients analyzed at each timepoint. [a]Based on time normalized number of attacks per 4 weeks. [b]1 month = 4 weeks. [c]Deucrictibant IR capsule, 10 mg twice daily. [d]Deucrictibant IR capsule, 20 mg twice daily.

Phase 1 studies with deucrictibant XR tablet

- In Phase 1 studies, deucrictibant XR tablet (40 mg):
  - Allowed for controlled release and absorption of deucrictibant in the small intestine and colon.[18]
  - Sustained mean concentrations in circulation above threshold levels of therapeutic exposure from ~1.5 to ≥24 hours post-dose.[18-20] Effective concentration estimated to provide 85% maximal response (EC_{85}) is 13.8 ng/mL.[18,19]
  - Showed more sustained exposure over time compared with twice-daily IR capsule (2 x 20 mg) used in proof-of-concept Phase 2 CHAPTER-1 study.[18-20]
- Maintenance of exposure through 24 hours supports once-daily dosing with XR tablet for prophylactic treatment.

Figure 2. Deucrictibant XR tablet maintains exposure above threshold level of therapeutic exposure for ≥24 hours

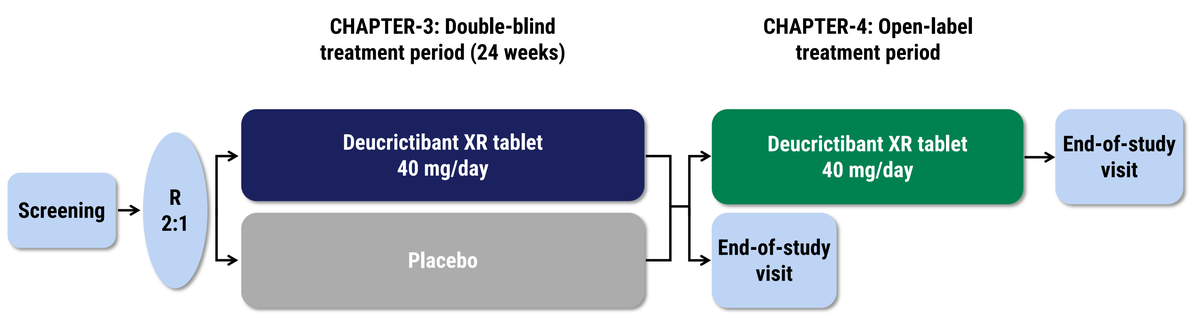


EC_{85}, concentration estimated to provide 85% maximal response; IR, immediate-release; SD, standard deviation; XR, extended-release. [a]Single oral dose of 2 x 20 mg deucrictibant IR capsule.

CHAPTER-3 study overview

- **CHAPTER-3 (NCT06669754):** an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of orally administered deucrictibant XR tablet once daily for prophylaxis of HAE attacks in adolescents and adults.
- **Target enrollment:** 81 adolescents and adults living with HAE.
- **Randomization:** 2:1 to receive deucrictibant XR tablet 40 mg or matching placebo once daily for 24 weeks. Stratified according to:
  - age group (≥12 to <18 years, ≥18 years) and
  - baseline HAE attack rate (1 to <2 attacks per 4 weeks, ≥2 attacks per 4 weeks).
- **Extension studies:** participants who complete the 24-week treatment period can elect to continue deucrictibant XR tablet treatment in the CHAPTER-4 (NCT06679881) open-label extension.[17]

Figure 3. CHAPTER-3 and CHAPTER-4 study design



R, randomization; XR, extended-release.

Participants

Table 1. CHAPTER-3 key inclusion and exclusion criteria

Key inclusion criteria include	Key exclusion criteria include
• Aged ≥12 years • Diagnosed with HAE • History of ≥3 HAE attacks within the 3 consecutive months prior to screening visit • Access and ability to use standard-of-care on-demand treatment to manage HAE attacks	• Participation in any other investigational drug study • Received prior HAE prophylactic treatment with deucrictibant • Receiving long-term prophylactic therapy for HAE within the specified time-period before screening: – 2 weeks: C1 inhibitor, berotralstat, or anti-fibrinolytic – 4 weeks: Attenuated androgen – 5 half-lives: Lanadelumab • Pregnant or breastfeeding

HAE, hereditary angioedema.

Objectives and endpoints

- **Primary objective:** evaluate efficacy of deucrictibant XR tablet for prevention of angioedema attacks vs placebo.
- **Secondary objectives:**
  - evaluate efficacy
  - evaluate safety and tolerability
  - evaluate pharmacokinetics
  - evaluate impact on health-related quality of life

Table 2. Study endpoints in CHAPTER-3

Primary endpoint	• Time-normalized (per 4 weeks) number of investigator-confirmed HAE attacks during the 24-week treatment period
Secondary efficacy endpoints	• Number of attacks treated with on-demand medication • Number of "moderate or severe" and "severe" attacks[a] • Proportion of participants achieving ≥50%, ≥70%, or ≥90% reduction in attack rate relative to baseline and proportion remaining attack free • Proportion of time without angioedema symptoms
Patient-reported outcomes	• Angioedema Quality of Life (AE-QoL) questionnaire • Patient Global Assessment of Change (PGA-Change) • Angioedema Control Test 4-week version (AECT-4wk) • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP) • Abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9)
Safety	• TEAEs including serious TEAEs and TEAEs leading to study drug discontinuation • Change from baseline in clinical laboratory tests, vital signs, and ECG parameters

ECG, electrocardiogram; HAE, hereditary angioedema; TEAE, treatment-emergent adverse event. [a]Moderate attacks defined as an HAE attack that limits/interferes with the participant's ability to attend work/school or participate in family life and social/recreational activities. Severe attack defined as an HAE attack that significantly limits the participant's ability to attend work/school or participate in family life and social/recreational activities.

This presentation includes data for an investigational product not yet approved by regulatory authorities.

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